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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
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08/484,340 06/07/95 SMITH

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EXAMINER

HM21/0323

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ART UNIT PAPER NUMBER

1634

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DATE MAILED: 03/23/98

This is a communication from the examiner in charge of your application.  
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 1/23/98 (cert of mailing)

☐ This action is FINAL.

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 75-77, 81-83, 88, 92-109, 109-132 is/are pending in the application.

Of the above, claim(s) 112-117 is/are withdrawn from consideration.

☐ Claim(s) is/are allowed.

☒ Claim(s) 75-77, 81-83, 88, 92-109, 109-111, 118-132 is/are rejected.

☐ Claim(s) is/are objected to.

☐ Claim(s) are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some\* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number)

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

\*Certified copies not received:

☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s)

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-

SEE OFFICE ACTION

08/484-5 FOLLOWING PAGES

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### **DETAILED ACTION**

1. This action is in response to papers filed 01/23/98 in which claims 73, 74, 78-80, 84-87, 89-91 were canceled, claims 75, 81, 88, 92, 109 were amended. Currently, claims 75-77, 81-83, 88, 92-107, 109-132 are pending. Claims 112-117 are withdrawn from further consideration as being drawn to a non-elected invention. All of the amendments and arguments have been thoroughly reviewed.
2. The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.
3. Any rejections not reiterated below are hereby withdrawn.

#### ***Claim Rejections - 35 USC § 112***

4. Claims 75-77, 81-83, 88, 92-107, 109-111, 118-132 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
  - a. Claims 118-129 are rejected as indefinite because these claims now depend from canceled claims. Clarification is required. In the interest of compact prosecution, it has been interpreted that claims 118-120 should depend from claim 75, claims 121-123 should depend from claim 81, claims 124-126 should depend from claim 88, and claims 127-129 should depend from claim 92.
  - b. Claims 75-77, 81-83, 88, 92-97, 101-107, 109-111, 118-132 are rejected as indefinite over the recitation "said chromophore or fluorophore attached" because it is unclear as

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to where, how and to what the label is attached. It is noted that the phrase "so as to allow chain extension by a polymerase" is an inherent property of any labeled primer with a free 3'OH. The rejection applied to claims 118-129 to the extent that they depend from claims 75, 81, 88 and 92.

c. Claims 75-77, 81-83, 92-107, 109-111, 118-130 are rejected as indefinite over the recitation "has been base-paired to a template" and "has been separated" for the following reasons. It is unclear as to whether the claims are drawn to an oligonucleotide primer itself or a primer extended and/or hybridized to a template. The phrase "has been", in past tense, makes the claims indefinite because it is unclear as to exactly when the primer was base-paired or extended or separated. The rejection applied to claims 118-129 to the extent that they depend from claims 75, 81 and 92.

d. Claims 98-100 are rejected as indefinite because it is not understood what is encompassed by the claims. The claim recites the primer comprises a first portion which has been hybridized to a template. The claims recites that the first portion "has been" extended. However, it is unclear as to whether the claim encompasses the oligonucleotide only containing a first portion, containing both the first portion and the second portion or containing the first and/or second portions and/or the template strand.

e. Claims 101-107, 109-111, 130-132 are rejected as indefinite over the recitation "The primer of claim 75, prepared by a method comprising the steps of providing a primer" because it is unclear if the primer provided is the same as that of base claim 75 or a different

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primer used to make the primer of claim 75. That is, the phrase “a primer” in the phrase “providing a primer” lacks proper antecedent basis.

f. Claims 101-107, 109-111, 130-132 are rejected as indefinite for the following reasons. It is unclear as to how the steps of providing a tagged primer and hybridization the primer to a complementary sequence constitutes a method of making a primer of base claim 75. It is unclear if the claim is intended to produce a double stranded oligonucleotide product from two single stranded products. It is noted that what is claimed is a product by process, the claim is drawn to a primer made by hybridizing a labeled primer to a complementary sequence but what is claimed is an oligonucleotide primer.

g. Claims 101-107, 109-111, 130-132 are rejected as indefinite over the recitation “hybridizing the primer to a sequence which is complementary” because it is unclear as to what the phrase “a sequence” refers to. It is unclear if the phrase means a particular sequence of another oligonucleotide, nucleic acid, polynucleotide complementary to the tagged primer. Sequence is not an art recognized term for an oligonucleotide, nucleic acid, polynucleotide but is generally reserved to refer to the makeup of the oligonucleotide, nucleic acid, polynucleotide. Thus it is unclear what is meant by “a sequence” in the claims.

h. Claims 94, 97, 100, 103, 107 are rejected as indefinite over the recitation “5' end or in the vicinity thereof” because the claims do not provide a definition of what is encompassed by the vicinity of the 5' end and therefore, the scope of the claims cannot be determined. Vicinity is a relative term that does not adequately describe the metes and bounds of the claim.

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i. Claim 105-107, 109-111 are rejected as indefinite over the recitation "the method comprising extending the primer of claim 101" because this phrase lacks proper antecedent basis. Claim 101 is drawn to a method that does not contain an extending step. Therefore it is unclear as to what method the phrase "the method" refers to.

j. Claim 109-111 is rejected as indefinite over the recitation "a method comprising use of the oligonucleotide of claim 105" because it is unclear as to whether the oligonucleotide of claim 105 is to be used as a primer for generating extended oligonucleotide fragments in the presence of ddNTPs or if the oligonucleotide of claim 105 is an extended product that is run on a gel and read to determine sequence. That is, the role of the oligonucleotide of claim 105 in the method of claim 109 is unclear.

k. Claims 110-111 are rejected as indefinite over the recitation "the performance" because this phrase lacks proper antecedent basis. This rejection could be overcome by amending the claim to recite "wherein performance".

l. Claim 111 is rejected as indefinite over the recitation "the primer includes all four chain termination DNA sequencing reactions" because it is unclear if the primer has in its sequence all of the chain terminating ddNTPs or if the primer is to be used in the presence of each chain terminating ddNTP so as to contain only one type of ddNTP.

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***Claim Rejections - 35 USC § 103***

5. Claims 75-77, 81-83, 88, 92-107, 109-111, 118-132 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kitamura *et al.* (*Proc. Natl. Acad. Sci., USA* (June 1980) 77:3196-3200) in view of Smith et al (U.S. Patent 5,171,534 (Dec. 15, 1992)). The rejection applied to claims 118-129 to the extent that they depend from claims 75, 81, 88 and 92.

Kitamura teaches a method of determining nucleic acid sequence where DNA is synthesized in the presence of a template, 5'-end labeled oligonucleotide, and unlabeled dNTPs and ddNTPs (abstract, Figure. 1, page 3197, first full paragraph) to form labeled primers, labeled extension products and labeled extension products/template duplexes. Kitamura teaches that the use of an end-labeled primer in lieu of labeled nucleotides improved the results of the method because the background was lowered and the end labeling method was less costly (page 3200, first paragraph).

Smith teaches the use of chromophore or fluorophore tagged oligonucleotide (col. 3 lines 17-18, col. 5 lines 3-24). Smith states that the primers used for the DNA sequencing reaction should have a free 3'OH, be complementary to a unique region of the target, be sufficiently long to specifically hybridize and that the chromophore or fluorophore label should not interfere with extension by the polymerase (col. 4, lines 46-55). Smith teaches the use of more than one label to distinguish sets of fragments (col. 4 lines 41-46, 63-67). Smith teaches the use of DNA primers. Smith teaches the hybridization of labeled primer to a template, extension to produce an extended

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primer, denaturation of the extended primer from the target, and detection of the extended primer by laser excitation (col. 5, lines 60-67, col. 6, line 17 . It is noted that the inventive entity of the Smith reference is different from that of the instant invention and therefore Smith qualifies as art under 102(e).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have substituted fluorophore or chromophore labels for the radioactive label of Kitamura to have improved the method of Kitamura by having obviated the need for hazardous and expensive chemicals with a limited half-life and to have permitted the method of Kitamura to be automated by using the apparatus taught by Smith to have detected the fluorophore or chromophore labeled fragments of Kitamura.

6. Claims 75-77, 81-83, 88, 92, 94-95, 97-98, 100-101, 103-105, 107, 109, 119-120, 122-123, 125-126, 128-129, 131-132 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kitamura in view of Langer *et al.* (*Proc. Natl. Acad. Sci., USA* (Nov. 1981) 78:6633-6637) and further in view of Leary *et al.* (*Proc. Natl. Acad. Sci., USA* (July 1983) 80:4045-4049). The rejection applied to claims 118-129 to the extent that they depend from claims 75, 81, 88 and 92.

Kitamura teaches a method of determining nucleic acid sequence where DNA is synthesized in the presence of a template, 5'-end labeled oligonucleotide, and unlabeled dNTPs and ddNTPs (abstract, Figure. 1, page 3197, first full paragraph) to form labeled primers, labeled extension products and labeled extension products/template duplexes. Kitamura teaches that the

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use of an end-labeled primer in lieu of labeled nucleotides improved the results of the method because the background was lowered and the end labeling method was less costly (page 3200, first paragraph).

Langer teaches making biotinylated nucleotides. Langer teaches that such probes containing biotin groups provide a suitable alternative to radioisotopes for nucleic acid detection (page 6633, first paragraph). Langer teaches that avidin can be coupled to an appropriate indicator molecules such as a fluorescent dye which will then specifically detect the biotinylated oligonucleotide (page 6633, first paragraph). Langer teaches that the modified nucleotide are substrates for polymerases and that oligonucleotide containing the biotinylated nucleotide have properties similar to those of unmodified oligonucleotide, including specifically and efficiently hybridization to complementary sequences (abstract & page 6637 first paragraph).

Leary teaches method of making biotinylated probes for use in hybridization reactions using nick translation methods (page 4046, paragraph bridging col. 1-2).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have substituted the fluorophore/avidin/biotinylated oligonucleotide label of Langer & Leary for the radioactive label of Kitamura to have improved the method of Kitamura by having obviated the need for hazardous and expensive radiochemicals with a limited half-life. One of ordinary skill in the art at the time the invention was made would have been motivated to have used the methods of Langer & Leary to have provided a biotinylated oligonucleotide probe where the probe was made by nick translation in the presence of a limited



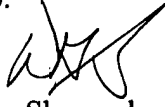
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number of biotinylated nucleotide analogs to have made a labeled oligonucleotide that could have then been detected using a fluorescently labeled avidin molecule, according to the teachings of Langer. Because of the teachings of Langer that such modified oligonucleotides behave nearly identical to their unmodified counterparts, the ordinary artisan would have had a reasonable expectation of success that such biotinylated oligonucleotides could have been used in the method of Kitamura and, as discussed above, would have improved the method of Kitamura by having obviated the need for radioactivity. It is noted that the instantly claimed invention does not specify how the the oligonucleotide are to be tagged or labeled, but only that there is a label "attached". The label of Langer & Leary which provides for nucleic acid detection using a fluorescent label/avidin/biotin system is considered to also be "attached" to the oligonucleotide and therefore renders the instantly claimed invention obvious.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Debra Shoemaker whose telephone number is (703) 305-4048 and by fax (703) 305-7401 for informal or draft papers. The examiner can normally be reached on 7:30 AM-5:00 PM from Monday to Thursday. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax phone number for this Group is (703) 305-3014 or (703) 308-4242 for official faxes.

Any inquiry of an a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

  
Debra Shoemaker  
March 10, 1998

  
W. GARY JONES  
SUPERVISORY PATENT EXAMINER

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3/13/98